Drug points

Generalised chorea due to digoxin toxicity

Drs L J M M MULDER, R C van der MAST, and J D MEERWALDT (University Hospital "Dijkzigt," 3015 GD Rotterdam, The Netherlands) write: Digoxin is a widely prescribed drug with narrow therapeutic margins, and intoxication is a common complication. We report a case of severe generalised chorea, agitation, and emotional disturbance due to digoxin excess.

A 63 year old woman with a dissection of the ascending aorta had been treated conservatively for one month with digoxin 250 μg daily, labetalol 100 mg three times a day, dihydralazine 25 mg twice a day, isosorbide mononitrate 20 mg three times a day, bromazepam 1·5 mg three times a day, and triamterene one capsule daily. During the operation the defect of the intima was reconstructed with a haemoshield prosthesis (anaesthetic: fentanyl 36 ml and pancuronium 18 mg). The patient was haemodynamically stable immediately afterwards. Postoperatively she was treated with digoxin 250 μg daily, triamterene one capsule daily, and, for three days, prednisolone acetate 25 mg daily. Three days after the operation she started to complain of extreme fatigue, showed no clouding of consciousness but was disoriented in time, appeared to be frightened, and had an impaired memory. Generalised symmetric choreatic movements increased in severity during the next few days to such an extent that she injured herself. The patient had neither been treated with neuroleptic drugs nor received other medication in the past which could have caused chorea. There was no history of rheumatic fever. Computed tomography of the brain without contrast enhancement showed no abnormalities. Extensive laboratory values were repeatedly within normal ranges, except for urea and creatinine, which were temporarily raised, consistent with transient renal failure. The digoxin value, which had not been recorded previously, was 34 μg/l (therapeutic range 10-26 μg/l) one week after surgery. Digoxin was then discontinued and she was treated successfully with oral haloperidol 5 mg daily for one month. After the tapering off of haloperidol the abnormal involuntary movements did not return (follow up two years).

There are only limited data on the relation between non-cardiac symptoms of digoxin toxicity and serum digitalis concentrations.[1] Above 30 μg/l (in our patient 34 μg/l) there is a high incidence of intoxication, especially with renal failure.[2] In contrast to a previously reported patient, who had hemichorea due to digoxin toxicity,[3] our patient had generalised symmetric chorea. After the withdrawal of digoxin haloperidol was discontinued and the choreatic movements did not return. The fact that haloperidol controlled the choreatic movements might suggest that digoxin toxicity induces a functional alteration in the activity of dopamine at the synaptic level.[4] The involvement of dopaminergic pathways might also explain the psychotic symptoms of digoxin intoxication, as in the more common organic brain syndromes.[5,6] Digoxin toxicity should be included in the differential diagnosis of iatrogenic choreatic disorders.

1 Smith TW, Antman EM, Friedman PL, Blatt CM, Marsh JD. Digitalis glycosides: mechanisms and manifestations of toxicity. *Prog Cardiovasc Dis* 1984;**26**:495-523.
2 Aronson JK. Digitalis intoxication. *Clin Sci* 1983;**64**:253-8.
3 Wedzicha JA, Lees AJ, Hoffbrand BI. Chorea in digoxin toxicity. *J Neurol Neurosurg Psychiatry* 1984;**47**:419.
4 Klawans HL, Werner WJ, eds. *Textbook of clinical neuropharmacology*. New York: Raven Press, 1981:49-67.
5 Closson RG. Visual hallucinations as the earliest symptom of digoxin intoxication. *Arch Neurol* 1983;**40**:386.
6 Cunnings JL. Organic psychosis. *Psychosomatics* 1988;**29**:16-26.

Neutropenia caused by intravenous immunoglobulin

Drs R V MAJER and P J GREEN (St Mary's Hospital, Portsmouth PO3 6AG) write: Intravenous immunoglobulin is becoming widely used in childhood idiopathic thrombocytopenic purpura[1]; we report two cases of reversible neutropenia occurring after each infusion of intravenous immunoglobulin.

A 6 year old boy developed an idiopathic autoimmune haemolytic anaemia which responded initially to corticosteroids and subsequently splenectomy. When aged 11 years he developed idiopathic thrombocytopenic purpura with a platelet count of $5{\cdot}0\times10^9$/l. Normal immunoglobulin (Sandoglobulin) 0·4 g/kg for five days restored his platelet count to normal for three weeks. The absolute neutrophil count fell from 7·55 to $0{\cdot}5\times10^9$/l by day 14. Two subsequent courses of normal immunoglobulin, 1 g/kg for two days and 0·4 g/kg for one day, were followed by nadirs in absolute neutrophil count of 0·05 and $0{\cdot}1\times10^9$/l respectively. The periods of neutropenia lasted for 7-10 days and then the count recovered spontaneously to normal levels as the platelet count began to decline. Troublesome mouth ulcers occurred during periods of neutropenia and immunoglobulin was therefore discontinued. The patient subsequently required corticosteroids to maintain a normal platelet count but relapsed three times on their withdrawal.

A 12 year old boy with idiopathic thrombocytopenic purpura gained a partial response from corticosteroids but relapsed on their withdrawal. Normal immunoglobulin 0·4 g/kg for five days restored his platelet count to normal for four weeks. Subsequent one day infusions of immunoglobulin 0·4 g/kg at four weekly intervals were required to maintain his platelet count at normal levels until a curative splenectomy was performed. His absolute neutrophil count fell after each course of intravenous immunoglobulin from previously normal levels to nadirs of 1·2, 1·8, 1·3, and $1{\cdot}3\times10^9$/l respectively and recovered spontaneously as the platelet count declined. The neutropenia occurred 7-14 days after each infusion and lasted for 14 days. No infective problems were seen.

The neutropenia followed every course of intravenous immunoglobulin given to the two patients and followed a distinct pattern: the neutrophil count fell 7-14 days after treatment, remained low for 7-14 days, and recovered spontaneously over the next seven days as the platelet count was beginning to fall. The neutropenia seen in both cases never recurred subsequently and presumably was due to a perturbation of the immune system caused by the intravenous immunoglobulin. Immunoglobulin is a relatively safe agent, side effects being limited to mild pyrexial or anaphylactoid reactions, particularly in selective IgA deficient individuals. This side effect has not been previously reported to the Committee on Safety of Medicines or to the manufacturer. Interestingly, there are two reports of successful treatment of autoimmune neutropenia using intravenous immunoglobulin.[2,3] Clearly neutrophil counts should be monitored when intravenous immunoglobulin is used.

1 Imbach P, Berchtold W, Hirt A, *et al.* Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. *Lancet* 1985;ii:464-8.
2 Pollack S, Cunningham-Rundles C, Smithwick EM, Baradun G, Good RA. High dose intravenous gammaglobulin for autoimmune neutropenia. *N Engl J Med* 1982;**307**:253.
3 Bussel JB, Lalezari P, Hilgartner MW, Purtin J, Fikrig S, O'Malley J. Reversal of neutropenia with intravenous gammaglobulin in auto-immune neutropenia of infancy. *Blood* 1983; **62**:398-400.

Purpuric rash associated with slow release morphine

Drs R J WHISTON, C D M GRIFFITH, and B R HOPKINSON (Queen's Medical Centre, Nottingham NH7 2UH) write: A 70 year old man required strong analgesics for stump pain after a below knee amputation performed for peripheral vascular disease. He was prescribed slow release morphine sulphate (MST, Napp Laboratories) 20 mg twice a day by mouth for pain relief, his other long term medication being salbutamol and beclomethasone inhalers for chronic obstructive airways disease. He was also receiving vitamin B_{12} injections for pernicious anaemia every two months.

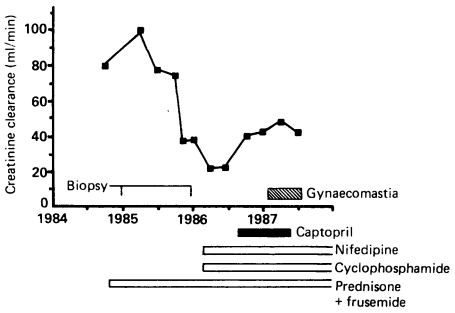
Ten days after starting morphine he developed a purpuric rash on the extensor surface of his thighs, buttocks, and trunk. His full blood count showed haemoglobin of 100 g/l, a white cell count of 10×10^9/l, and a platelet count of 455×10^9/l with an erythrocyte sedimentation rate of 12 mm in the first hour. Blood cultures were performed to eliminate sepsis as a cause of rash and were sterile. Echocardiography showed no evidence of mural thrombus or valve disease consistent with distal embolisation or infective endocarditis. After these negative investigations we attributed his rash to the morphine, which was stopped, resulting in fading of the rash after 48 hours.

The opiate analgesics have many well known side effects but are only rarely associated with skin eruptions. We believe this to be the first reported case of an extensive rash associated with morphine sulphate. Napp Laboratories and the Committee on Safety of Medicines have no recorded cases of rash after administration of morphine sulphate. There have been three reported incidents of rash associated with dihydrocodeine reported to the committee.

Gynaecomastia associated with captopril

Drs H M MARKUSSE and R H B MEYBOOM (Department of Rheumatology, University Hospital, 2300 RC Leiden, The Netherlands) write: Captopril is associated with a wide variety of side effects including hypotensive episodes, granulocytopenia, proteinuria, loss of taste, angio-oedema, and coughing.[1] We report the first case of gynaecomastia associated with the use of captopril.

A 34 year old man suffered from systemic lupus erythematosus and mild biopsy proved mesangial glomerulonephritis with proteinuria and oedema, for which he had been treated with frusemide and low dose prednisone since 1984 (figure). A second renal



Time course of creatinine clearance and gynaecomastia in relation to administration of captopril, nifedipine, cyclophosphamide, prednisone, and frusemide.

biopsy, performed because of a deterioration in his renal function, showed diffuse proliferative glomerulonephritis. The renal function deteriorated further despite treatment with prednisone 60 mg a day and azathioprine, so monthly intravenous pulse therapy with cyclophosphamide (1000 mg) was started. The hypertension could not be controlled by nifedipine, but after captopril was given at 75 mg a day blood pressure returned to normal. Seven months later a painful gynaecomastia developed gradually on the left side. Normal values were obtained for liver enzymes, serum thyroxine, prolactin, testosterone, oestrone, and oestradiol, and 24 hour urinary excretion of 17 ketosteroids. Captopril was stopped, the left mamillary pain vanished within two weeks, and over the following weeks the breast enlargement disappeared completely. No endocrine abnormalities were found and other causes of breast enlargement such as alcoholism, diabetes mellitus, and liver disease were excluded.

There are several reports of breast enlargement in women induced by penicillamine,[2] which is a second line antirheumatic drug with a molecular structure related to that of captopril. Both compounds contain a sulphydryl group at one end of the molecule separated by a short chain of carbon atoms from an acid group at the other end. Both drugs bind copper, and they produce similar adverse side effects such as rash, nausea, loss of taste, proteinuria, and neutropenia. One case of penicillamine induced breast enlargement in a man has been reported,[3] which showed a strong resemblance to our case. No gynaecomastia associated with captopril has been reported to the manufacturers or to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs. The clinical course of this patient's gynaecomastia, the absence of hormonal disturbances, and the similarity between captopril and penicillamine, a drug with a possible breast enlarging action, suggest that in this case gynaecomastia was induced by captopril.

1 Edwards IR, Coulter DM, Beasley DMG, Macintosh D. Captopril: 4 years of post marketing surveillance of all patients in New Zealand. *Br J Clin Pharmacol* 1987;23:529-36.
2 Kahl LE, Medsger TA, Klein I. Massive breast enlargement in a patient receiving d-penicillamine for systemic sclerosis. *J Rheumatol* 1985;12:990-1.
3 Reid DM, Martynoga AG, Nuki G. Reversible gynaecomastia associated with D-penicillamine in a man with rheumatoid arthritis. *Br Med J* 1982;285:1083-5.

Points

Griffiths on community care

Dr B R W Lodge (Carlton Hayes Hospital, Narborough, Leicestershire LE9 5ES) writes: Elderly people and people with mental health problems are not synonymous with people requiring "ongoing care." Both groups may need acute or continuing care, or both, of a medical or social type. In their own homes people need a range of care from intensive health care to intensive social care, but at every point there are proportions of need from health and local authorities. The division between health and local authority financed care advocated by the Griffiths report is not helpful, and "a budget for care" would be better managed jointly than through a single authority. Much progress has been made recently through health, social services, housing, and voluntary agencies working together both in planning and in community teams: these have promoted economic service provision and joint assessments of individuals that can pinpoint their needs. The proposed care manager should be jointly financed. There are, for example, merits in one person doing both housework and basic nursing (as in the Darlington scheme), thereby bridging the gap between two authorities.

Professor Michael D Warren (Canterbury CT4 5AZ) writes: Professor Elaine Murphy (26 March, p 876) emphasises that the proposed new arrangements for community care must ensure that no local authority can ignore its responsibilities. Additional safeguards are required. The report emphasises the requirement for social services authorities to identify and assess individuals' needs and the community care needs of their locality "within the resources available." Experience has shown—for example, in assessing eligibility for the attendance allowance—that wide variations occur in the assessments made by different people of the same disabled person, even when external constraints of resources are disregarded. As social workers are to be given the difficult task of making the assessment and arranging the "packages of care" within the income and capital of the person and of the publicly allocated resources, some appeal machinery must be introduced for those who feel they have been wrongly assessed or who disagree with the proposed package and its related expenditure. The current, extensively documented, inadequacies of community care continue despite provisions similar to some of the recommendations of the Griffiths report in the Disabled Persons (Services, Consultation and Representation) Act 1986 and the earlier Chronically Sick and Disabled Persons Act 1970 and the existence of a minister for the disabled since 1974. The government should act now to enable and encourage social services authorities to enlarge and improve their community care services especially by introducing a specific block grant. Much can be done now by implementing fully existing legislation relating to people with disabilities, none of which is referred to in the Griffiths report.

Transporting critically ill patients

Dr P Meyer (SAMU des Yvelines, 78150 Le Chesnay, France) writes: In their description of transporting critically ill patients by ordinary ambulance Dr J F Bion and coworkers (16 January, p 170) described disrupted monitoring during the 30 minute journey; all patients needing assisted ventilation were manually ventilated. Even during intrahospital moves critically ill patients are particularly at risk of cardiac rhythm disturbances and blood pressure variations related to hypoxaemia and changes in acid-base state.[1,2] These complications could be prevented in the presence of trained physicians by close monitoring of cardiac rhythm and blood pressure.[3] In our institution, as elsewhere in France, transport of critically ill intubated patients, even for short interhospital transfers, has always been performed over the past 10 years by medical mobile care units supplied with the same equipment as the intensive care unit.[4] Doctors with special training in anaesthesia are in charge of such transports. The community is responsible for this medical transport system, whose cost each year amounts to US $1 per head. Like Dr Bion and colleagues, we think that such a policy should be associated with improved training in resuscitation for non-specialist physicians.

1 Braman SS, Dunn SM, Amico CA, Millman RP. Complications of intra-hospital transport in critically ill patients. *Ann Intern Med* 1987;107:469-73.
2 Insel J, Weissman C, Kemper M, Askanazi J, Hyman AI. Cardiovascular changes during transport of critically ill and postoperative patients. *Crit Care Med* 1986;14:539-41.
3 Ehrenwerth J, Sorbo S, Hacker A. Transport of the critically ill adult. *Crit Care Med* 1986;14:543-7.
4 Herve C, Gaillard M, Huguenard P. Early medical care and mortality in polytrauma. *J Trauma* 1987;27:1279-85.

Late life depression: undertreated?

Dr H P Rosenvinge (Moorgreen Hospital, Southampton SO3 3JB) writes: Drs S Soni and J Shrimankar (26 March, p 930) advise caution when using tricyclic antidepressants for depressive symptoms in dementia. They base this on their study of a population of mean age 79. The incidence of side effects was high. A daily dose of 150 mg of amitriptyline, described as a "full therapeutic" dose, was given to all patients. The impression that this is standard practice in the elderly is misleading and potentially worrying. Smaller doses of tricyclics are required in the elderly. A dose of 25-50 mg of amitriptyline daily may be used with good effect and minimum side effects. Let us not condemn a useful form of treatment by adopting excessive and often poorly tolerated doses.

Dr Som D Soni (Prestwich Hospital, Manchester M25 7BL) replies: The "standard practice" mentioned by Dr Rosenvinge of prescribing small doses of tricyclics for elderly depressed patients must reflect the caution that psychogeriatricians already show about using these drugs. In other situations such doses would be considered to be subtherapeutic, and studies of concentrations in serum, at least with nortriptyline,[1] suggest a therapeutic window effect and a threshold below which antidepressants give a poor clinical response.

The caution that we advised applied to a minority of elderly patients with depression, who may also have cognitive dysfunction. In our research[2] we had a control group of elderly depressed patients who did not have dementia, and these patients, without exception, tolerated the tricyclics well. If the cholinergic mechanisms in the brains of demented patients are already jeopardised because of the underlying disease it is reasonable to show caution in prescribing drugs which may cause further deterioration. There are other forms of treatment, such as electroconvulsive therapy and tetracyclic agents, which are at least as effective as tricyclic antidepressants.

1 Asberg M, Cronholm B, Sjoquist F, Tuck D. Relationship between plasma level and therapeutic effect of nortriptyline. *Br Med J* 1977;iii:331.
2 Shrimankar J, Soni SD, Sampath G. Dexamethasone suppression test and response to antidepressant therapy in psychogeriatric patients. *Acta Psychiatr Scand* (in press).

How informed is signed consent?

Dr Diane E Wallis (Cardiff CF2 6LN) writes: It was not very surprising to read that such a high percentage of the patients of Mr D J Byrne and others (19 March, p 839) had little idea of the nature of the operation they had just undergone. What was surprising was that the authors did not believe that lack of communication skills and time on the part of the medical attendants was likely to be the major factor behind this. Patients usually arrive on a surgical ward for an elective procedure in a nervous state having had little information given to them as outpatients. Surely the appropriate recommendation is that patients should be well informed before admission to hospital and that time should be set aside both at the outpatient clinic when they are put on the list and in the hospital ward before the operation for a member of the surgical team to have an unhurried discussion with them.

Home visiting by consultants

Dr Dallas Brodie (chairman, Hospital Junior Staff Committee, British Medical Association, London WC1H 9JP) writes: Dr J M Grimshaw and colleagues (2 April, p 1003) conclude that home visiting is an important element of training for junior doctors attached to a geriatric unit and that home visiting by junior staff may be a cost effective alternative means of extending geriatric services into the community. My committee is aware of the importance of domiciliary consultations both for training purposes and to provide an extension of the services available from consultants. In an effort to encourage the extension of this facility we have been attempting to negotiate payment of domiciliary visit fees to senior registrars. I would be interested to learn whether any other specialties or centres share the view of your correspondents.

Osteoporosis in elderly Chinese

Dr Edith M C Lau (Department of Community Medicine, Chinese University of Hong Kong) writes: Dr Tessa Richards (5 March, p 659) states that osteoporosis is rare among elderly Chinese, probably on the basis of an ad hoc survey in 1970, which showed a low incidence of hip fracture in Hong Kong.[1] The problem has increased in the past 20 years. In a survey conducted in the Kowloon region of Hong Kong in 1985 the age specific rate was calculated to be 10 per 1000 in women aged 70 years and over. This agreed with findings of Pun and Young, who reported six new admissions with fractured neck of femur every day to a hospital which served one million people on Hong Kong Island.[2] Hong Kong has undergone dramatic urbanisation in the past 20 years and it seems that the increasing incidence is due to changes in environment and lifestyle. Maintaining a healthy lifestyle is as important in aging Asian populations as in the West.

1 Chalmers J, Ho KC. Geographical variations in senile osteoporosis. *J Bone Joint Surg [Br]* 1970;52:667-75.
2 Pun KK, Young RTT. Osteoporosis—the silent epidemic. *JAMA* (South East Asian edition) 1987 October:5-6.

A slip of the knife

Sir Charles Illingworth (Glasgow G12 0QB) writes: I suppose that I should be grateful to your anonymous correspondent who has written such a favourable review on my autobiography (9 April, p 1062), but he has made two factual errors. The surgeon who circumcised the boy with tonsillitis was James Duguid (later professor of pathology in Newcastle). I administered the anaesthetic—I was a third year student at the time. Also, Tenovus Scotland does not raise funds for cancer research but for many diseases other than cancer.

Ammonia burns of the eye

Professor Oliver Wrong (Department of Medicine, Rayne Institute, University College, London WC1E 6JJ) writes: Messrs J D L Beare, R S Wilson, and R J Marsh (27 February, p 590) attribute the rapid diffusion of ammonia through the cornea to its "high lipid solubility." This is a common but erroneous belief. The solubility of ammonia in lipids is only 0·5-25% of its solubility in water,[1,2] and those investigating its high diffusibility in body tissues have agreed that this cannot be due to a high lipid solubility.[2,3]

1 National Research Council. *International critical tables of numerical data, physics, chemistry and technology*. Vol 3 and 4. New York: McGraw Hill, 1928.
2 Good DW, Knepper MA. Ammonia transport in the mammalian kidney. *Am J Physiol* 1985;248:459-71.
3 Bourke E, Asatoor AM, Milne MD. Mechanisms of excretion of some low-molecular-weight bases in the rat. *Clin Sci* 1972;42:635-42.